

# **EXHIBIT 15**



## ATSDR: Perfluoroalkyl and Polyfluoroalkyl Substances (PFAS) Information for Clinicians (1/18/17)

available at: [https://www.atsdr.cdc.gov/pfc/videos/PFAS\\_Presentation.mp4](https://www.atsdr.cdc.gov/pfc/videos/PFAS_Presentation.mp4)

This presentation is designed by the Agency for Toxic Substances and Disease Registry, ATSDR, to familiarize health care providers about perfluorinated and polyfluorinated compounds, abbreviated P-F-A-S, "PFAS" provide guidance in areas of patient management, and share strategies on addressing potential patient concerns. You may want to review the document "An Overview of Perfluoroalkyl and Polyfluoroalkyl Substances and Interim Guidance for Clinicians Responding to Patient Exposure Concerns" developed by ATSDR along with this presentation.

### **Perfluoroalkyl and Polyfluoroalkyl Substances (PFAS): Information for Clinicians**

National Center for Environmental Health  
Agency for Toxic Substances and Disease Registry

CDC ATSDR

EXHIBIT

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To begin this presentation, we will define PFAS and describe their basic structure and chemical properties. We will address their presence and persistence both in the environment and in the human body, touch on current environmental reduction strategies, and explain different routes or modes of exposure.

Next, we will discuss some of the current research in order to gain perspective on what is known regarding PFAS before we discuss the potential health effects.

We will also point out research gaps regarding particular health effects and risk groups and examine where further study is needed.

Finally, we will present patient management strategies, which include risk assessment, use of biomonitoring to demonstrate population-wide exposure, effective communication, and risk reduction activities.

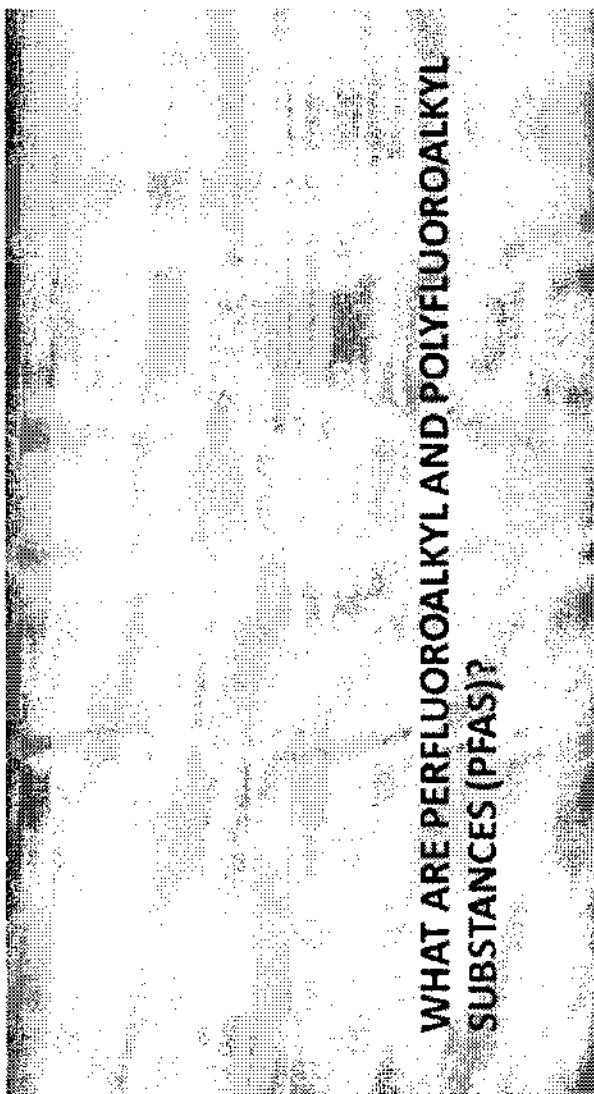
We will conclude by addressing some common concerns voiced by potentially exposed populations.

## Overview

- What are PFAS?
- Potential health effects of PFAS
- Addressing patient concerns



So, what are per- and polyfluoroalkyl substances?





Perfluoroalkyls and polyfluoroalkyls, referred to as PFAS and sometimes as P-F-Cs, are a family of synthetic chemicals used for nearly 70 years to make products that resist heat, oil, stains, grease, and water. They are commonly categorized into two structural groups: carboxylic acids such as perfluorooctanoic acid (PFOA) and sulfonates including perfluorooctane sulfonate (PFOS). These substances are unique in that they are both hydrophobic and lipophobic and as a result, these substances have many applications in industry. These chemicals are highly stable and resistant to environmental degradation. Due to their chemical stability, the presence of these compounds persists for many years once introduced into the environment. Continued exposure through contaminated water leads to bioaccumulation in fish, ingestion of which, provides a route of human exposure.

### Primary PFAS Structural Groups

## Two main groups

- Carboxylic acids (perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA))
- Sulfonates (perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS), perfluorobutane sulfonate (PFBS))

## Properties

- Carbon chain surrounded by fluorine atoms and acid group
- Repel water and oil
- Surfactants and dispersants
- Persistent, bioaccumulative





PFAS have many different uses. These chemicals may be used in the production of cookware to reduce stickiness, sofas and carpets to prevent staining, clothes and mattresses to make them waterproof, packaging to store food, and materials to fight fires. Because they help reduce friction, they are also used in a variety of other industries including: aerospace, automotive, building and construction, and electronics. In 2006, the Environmental Protection Agency, EPA, initiated the PFOA Stewardship Program in which eight major companies committed to reduce both facility emissions and product content of PFOA and related chemicals on a global basis. Additionally, the EPA established Significant New Use Rules for PFOA, requiring evaluation of any proposed new use of PFOA. These actions have drastically reduced the utilization of PFAS.

## PFAS Uses

### Main Uses

- Non-stick cookware,
- Carpet and clothing treatments,
- Paper and cardboard packaging, and
- Aqueous Film Forming Foam (AFFF) fire-fighting foam



For the general population, ingestion is considered the primary exposure pathway. This can occur through drinking contaminated water, ingesting fish and wildlife contaminated with PFAS, and until recently ingesting food contaminated by materials containing PFAS such as popcorn bags, fast food containers, non-stick cookware, and pizza boxes. Workers in industries or activities that manufacture, manipulate, or use products containing PFAS may be exposed to higher levels than the general population. Workers in facilities that historically used PFAS may also be exposed due to persistence of the compounds in the environment. For toddlers, hand-to-mouth transfer from surfaces treated with stain protectants containing PFAS, such as carpets, is thought to be the most contributory source of exposure. PFAS have also been detected in breast milk which may be another potential source of exposure for the youngest children in this age group

## **PFAS Exposure**

### **Major exposure pathways**

- Drinking contaminated water,
- Ingesting contaminated food,
- Workers in industries or activities that manufacture, manipulate, or use products containing PFAS, and
- Hand-to-mouth transfer from surfaces treated with stain protectants containing PFAS.



PFOA and PFOS are the 2 most commonly studied PFAS. The EPA has published a lifetime health advisory recommending that the concentration of PFOA and PFOS in drinking water, either individually or combined, should not exceed 70 parts per trillion. Health advisories published by the EPA are based on peer-reviewed literature of the effects of PFAS on laboratory animals, as well as epidemiological studies of human populations that have been exposed to PFAS. Investigated health outcomes include cancer, organ damage, and other health effects, as well as how they affect special populations including: pregnant women, fetuses, and children. The goal of an EPA lifetime health advisory is to provide Americans, including the most sensitive populations, with a margin of protection from a lifetime of exposure to PFOA and PFOS from drinking water. Health advisories are non-regulatory recommendations and are not enforceable. Public health advisories are designed as recommended federal guidance, so individual states may use more stringent contaminant levels.

### **PFAS in Drinking Water**

- Environmental Protection Agency (EPA) lifetime health advisory recommends that the concentration of PFOA and PFOS in drinking water, individually or combined, should not exceed 70 parts per trillion.
- EPA health advisories are non-regulatory but provide important recommendations.



The biologic half-lives of these agents in humans is generally several years. Different types of PFAS have different serum half-lives, as presented in this table. Because PFAS are common in routinely-used products, particularly those manufactured prior to 2006, most of the U.S. population experiences on-going exposure, resulting in continuous PFAS body burden. Due to efforts in reducing utilization and dispersal of PFAS through the Stewardship Program and the Significant New Use Rules, its presence in the environment is expected to decrease. This is expected to result in decreased on-going human exposure, which in turn will reduce PFAS levels in the general population. However, this reduction of biologic levels of PFAS will likely take many years due to the slow elimination of these compounds.

### Biological Persistence in Humans

Substance	Half-life
Perfluorooctanoic acid (PFOA)	3.8 years
Perfluorooctanesulfonate (PFOS)	5.4 years
Perfluorohexane sulfonic acid (PFHxS)	8.5 years
Perfluorobutane sulfonate (PFBS)	0.1 years



### **PFAS Elimination in Humans**

- Primarily eliminated mainly in urine
- Shorter chain PFAS tend to be eliminated faster than long chain PFAS
- Intersexual variability in elimination times exists

PFAS are not metabolized in the body but instead are eliminated very slowly through the urine. PFAS is present in bile, but undergoes significant enterohepatic circulation, contributing to its persistence in the body and reducing the contribution of this elimination route. Shorter chain PFAS tend to be eliminated faster from the body than long chain PFAS. There is also substantial variability between males and females concerning rates of elimination. One example of this is males have been found to have statistically significant higher amounts of PFOA in urine suggesting faster elimination of PFOA in males, but this relationship is not consistent for all PFAS. The same study found no difference in urinary PFOS concentration between the sexes. Additionally, lactation and menstruation present unique routes of elimination, which may increase elimination rates in females of reproductive age.



As briefly mentioned previously, breastfeeding is another exposure pathway of concern to families. PFOS and PFOA are commonly found in breastmilk and cord blood. Background levels have been steadily declining over the last decade, but the wide-spread past use and environmental presence reflects the ubiquity and persistence of these agents in our environment. The movement of PFAS from blood into different areas of the body, including into breastmilk and across the placenta, varies depending on the particular substance. Depending on the specific PFAS, breastmilk concentrations reflect roughly 3% to 10% of maternal serum concentrations. It is worth noting that cessation of exposure of the mother to PFAS will not be immediately reflected in maternal serum or breastmilk concentrations due to the long serum half-lives of PFAS. This represents a temporary source of increased exposure to breastfeeding infants. However, no consistent developmental health effects have been demonstrated in either population cohorts or occupational exposure groups. The benefits of breastfeeding, including: immunologic advantages, lower obesity rates, and greater cognitive development for the infant as well as a variety of health advantages for the lactating mother, greatly outweigh any potential risk posed by PFAS exposure through breastfeeding. The science on the health effects of PFAS for mothers and babies is evolving. However, given the scientific understanding at this time, the benefits of breastfeeding a baby outweigh those of not breastfeeding. The take home message here is that current evidence does not support discontinuing breastfeeding due to potential PFAS exposure. This is in accordance with recommendations from the World Health

### **PFAS in Breastmilk and Cord Blood**

- PFOS and PFOA are present in breastmilk and cord blood
- PFOS are more commonly detected than PFOA in breastmilk
- Milk concentrations typically are 3% to 10% of maternal serum concentration



Organization, the U.S. Surgeon General, and the American Academy of Pediatrics when the risk-benefit has been examined for other agents that are transferred through breastfeeding.

The National Health and Nutrition Examination Survey (NHANES) is a survey designed to assess the health and nutritional status of adults and children in the United States through the use of questionnaires, examinations, and biomonitoring. Biospecimens have been collected from healthy, asymptomatic NHANES participants since the 1980s, which includes data regarding PFAS since 1999. These data generally demonstrate steadily declining serum concentrations of PFOA and PFOS in the representative U.S. population. This decline most likely reflects efforts to eliminate the production and use of these chemicals in the last decade.

### PFAS in the U.S. Population

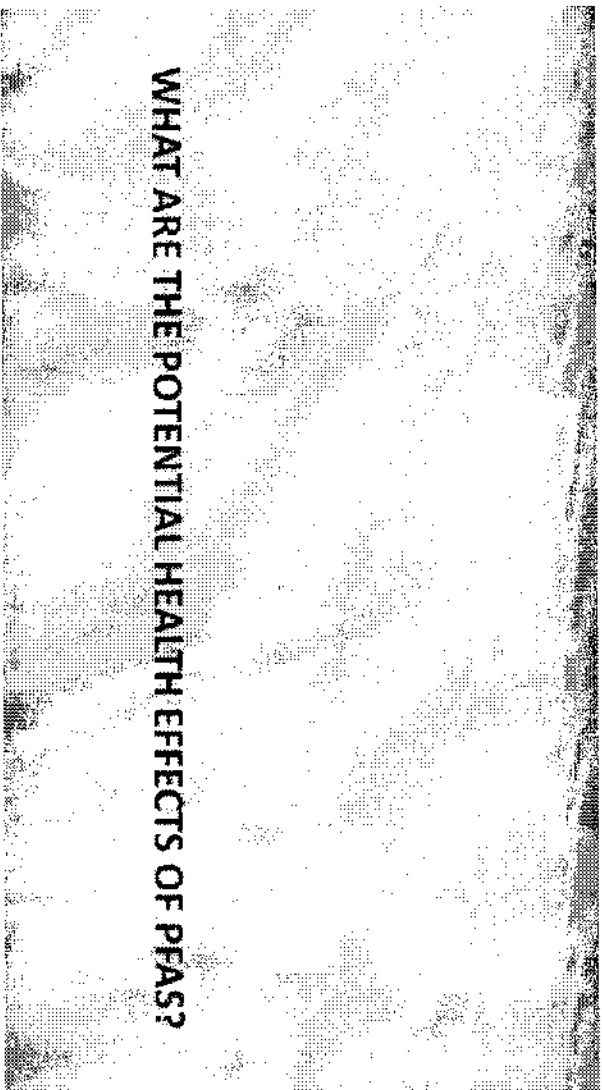
NHANES designed to assess the health and nutritional status of adults and children in the U.S. through biomonitoring reports on serum PFAS concentrations.

- 1999-2000 mean PFOA 5.2 and PFOS 30.4 ng/mL\* (n=1562)
- 2005-2006 mean PFOA 3.92 and PFOS 17.1 ng/mL (n=2120)
- 2011-2012 mean PFOA 2.08 and PFOS 6.31 ng/mL (n=1904)

\*ng/mL = µg/L = ppb



In this next section, we will discuss research regarding the potential health effects of PFAS.





Animal research, primarily utilizing rodent models, is the foundation of all toxicological study on health effects. Animal studies to date demonstrate a wide range of health effects following exposure to PFAS including liver enlargement, changes in serum lipid and cholesterol concentrations, reduced body weight, changes in thyroid hormone levels, reduced testosterone synthesis, suppression of antibody response, tumor formation, and developmental effects, including low birthweight, in offspring. These effects are demonstrated only at doses several orders of magnitude higher than any known human exposure level. It is important to note these studies present several limitations and cannot necessarily be extrapolated to human health effects. Toxicodynamic and toxicokinetic mechanisms vary drastically between humans and animals. For example, elimination of PFAS occurs much faster in rodents, as rodents demonstrate half-lives of days to weeks as compared to the human's years. However, animal studies may provide helpful clues regarding target organs for pathology or potential cancer risk.

## Animal Studies

Wide range of potential health effects including:

- Liver enlargement,
- Changes in serum lipid and cholesterol concentrations,
- Reduced body weight,
- Changes in thyroid hormone levels,
- Reduced testosterone synthesis,
- Suppression of antibody response,
- Tumor formation, and
- Developmental effects in offspring.



In animal studies, there is evidence of pancreatic, liver, and testicular adenoma formation following PFOA exposure. Without a better mechanistic understanding of both toxicokinetics and toxicodynamics, it is difficult to relate outcomes in animals to human health effects.

### **Non-cancerous Tumor Formation in Animals Following Exposure to PFAS**

#### **PFOA exposure in rodents**

- Pancreatic
- Liver
- Testicular



Data collected via the C8 Health Project has given researchers invaluable information on the human health effects of PFAS. The C8 Health Project was a large epidemiological study conducted because drinking water in six districts near Parkersburg, West Virginia were contaminated by release of PFOA, also called C8, from the 1950s until 2002. The study included 69,030 persons greater than or equal to 18 years of age.

### **C8 (PFOA) Health Project**

- Drinking water in six districts near Parkersburg, West Virginia were contaminated by PFOA (C8) from the 1950s through 2002
- Collected health and exposure data from communities potentially affected by PFOA contamination
- Data collected from 2005-2013, sampling 69,030 adults ( $\geq 18$  years of age)



The C8 science panel analyzed study data and found so-called "probable links" between elevated PFOA blood concentrations and the following: changes to thyroid function, high cholesterol, elevated blood pressure during pregnancy, ulcerative colitis, testicular cancer, and kidney cancer. Residents in the area of these releases showed PFOA concentrations in blood 5 times higher than those found in the NHANES biomonitoring of a representative sample of the U.S. population. Although associations were found between C8 exposure and elevations of liver enzymes and uric acid, potential markers for liver and renal disease, respectively, investigations did not reveal a probable link between C8 exposure and liver or renal disease. Similarly, despite establishing a probable link between C8 exposure and high cholesterol, a known risk factor for heart disease, there was no probable link revealed between C8 exposure and heart disease. Further research is needed to investigate the clinical implications of these observed changes to laboratory values.

## C8 (PFOA) Health Project

### Probable link\*

- Thyroid disease (potential to affect T4 and TSH levels)
- High cholesterol
- Pregnancy-induced hypertension
- Ulcerative colitis
- Testicular cancer
- Kidney cancer

\* A "probable link" in this setting is defined in the Settlement Agreement to mean that given the available scientific evidence, it is more likely than not that among class members a connection exists between PFOA exposure and a particular human disease.



There was not a clear association for either hyper- or hypothyroidism but rather inconsistent and weak trends of subclinical hyperthyroidism in women and subclinical hypothyroidism in men. These alterations to laboratory values do not equate to clinical disease. The majority of epidemiological studies demonstrated strong associations between PFOA and PFOS concentrations and total cholesterol in workers exposed to PFAS, and residents of communities with higher levels of PFOA in the drinking water compared to NHANES. However, these findings were not universally supported across all studies. Pregnancy-induced hypertension and pre-eclampsia were investigated separately. Cases of pregnancy-induced hypertension were identified by review of birth records, which relies on completion of birth records for all pregnancies and accurate identification and reporting of all cases. Cases of pre-eclampsia were identified by self-reporting, which introduces potential reporting and recall biases. Additionally, several potential confounders, such as exposure to other environmental toxins, for example, were not accounted for, and most odds ratios included confidence intervals which make the association statistically insignificant. This calls into question the validity of an association between PFAS exposure and pregnancy-induced hypertension. Understanding these limitations can help guide future areas of research study design on health effects.

## Some Limitations of C8 Results

### Thyroid Disease

- Subclinical measures (TSH, free thyroxine index)
- Lack of coherence among studies (high and low measurements)

### High Cholesterol

- The majority of epidemiological studies demonstrated strong associations between serum PFOA and PFOS concentrations and total cholesterol.
- Other studies have found no association between PFAS exposures and the total cholesterol levels.

### Pregnancy-induced Hypertension and Pre-eclampsia

- Review of birth records (PIH) and self-reporting (PE)
- Potential confounding
- Uncertainty regarding size of effect



In order to evaluate PFAS as a possible class of endocrine-disrupting chemicals, a number of studies have looked at potential reproductive effects. The Longitudinal Investigation of Fertility and the Environment (LIFE) study published in 2015 recruited 501 couples discontinuing contraception from two U.S. geographic regions from 2005 through 2009. Baseline interviews and anthropometric assessments were conducted, followed by blood collection for the quantification of seven serum PFAS (perfluorosulfonates, perfluorocarboxylates, and perfluorosulfonamides). This study concluded that perfluorooctane sulfonamide (PFOSA) was associated with smaller sperm head area and circumference, a lower percentage of DNA stainability, and a high percentage of bicephalic and immature sperm. A Danish cohort study evaluated plasma concentration of PFOS and PFOA among 1,240 women from the Danish National Birth Cohort recruited from 1996 to 2002. Women with the highest exposure to PFOS and PFOA had a longer time to pregnancy (TTP) and increased odds of infertility, defined as TTP >12 months. This association did not reach statistical significance for nulliparous women. These findings suggest that PFOA and PFOS exposure at plasma concentrations seen in the general population may reduce fecundity. Further research is needed to establish a more definite relationship.

## Reproductive Effects

- Limited number of studies
- The Longitudinal Investigation of Fertility and the Environment (LIFE) study: evaluated PFAS and human semen quality
- Danish National Birth Cohort: evaluated PFAS plasma concentrations and fecundity
  - Longer time to pregnancy was associated with higher maternal concentrations of PFOA and PFOS in multiparous women.
- Further research is needed



The association between PFAS and pregnancy outcome in an area with elevated exposure to PFOA from drinking water contaminated by a chemical plant releases was evaluated. The association between PFOA and the odds of miscarriage, stillbirth, preeclampsia, pre-term birth, term low birthweight, and birth defects, controlling for calendar time, age, parity, education, and smoking was evaluated. The authors found no associations between estimated serum PFOA levels and any adverse pregnancy outcomes other than possibly preeclampsia. The main limitations of this study are exposure reconstruction and self-reported pregnancy. The Norwegian Mother and Child Cohort Study (MoBa), evaluated the association between maternal plasma samples obtained around 17 weeks of gestation and birth weight, preterm birth, small for gestational age, and large for gestational age. A slight decrease in birth weight was found when comparing babies born to women with the highest exposure compared to the lowest levels of PFOS and PFOA. However, no clear evidence of an association with small for gestational age was observed. PFOS and PFOA were associated with decreased adjusted odds of preterm birth. Further research is needed to investigate the possible effects of PFAS on pregnancy outcomes.

## Pregnancy Outcomes

- Limited number of studies
- Main outcomes assessed by studies:
  - Stillbirth
  - Preeclampsia
  - Preterm birth
  - Term low birthweight
  - Birth defects
- No consistent associations were observed between serum PFAS and the outcomes listed above



On the basis of epidemiologic data, the C8 Science panel determined that there was a probable link between ulcerative colitis and occupational exposure to PFOA. Data were limited by small numbers. The incidence of ulcerative colitis demonstrated a statistically significant increase with exposure to PFOA. Other autoimmune diseases, including rheumatoid arthritis, lupus, type I diabetes, Crohn's disease, and multiple sclerosis, were investigated for association with PFAS exposure. No probable link was found between PFAS exposure and any other autoimmune disease.

## **PFOA and Autoimmune Disease**

### **Probable link to PFOA exposure:**

- Ulcerative Colitis

### **No probable link to PFOA exposure:**

- Rheumatoid arthritis
- Lupus
- Type I diabetes
- Crohn's disease
- Multiple sclerosis



There is strong evidence of suppression of the antibody response to an immune challenge in mice, demonstrated individually for PFOA and PFOS. Increasing concentrations of either substance consistently results in decreased primary antibody response in experimental studies. The results of available literature present a consistent pattern of findings that higher prenatal, childhood, and adult serum concentrations of both PFOA and PFOS were associated with suppression in at least one measure of the anti-vaccine antibody response to common vaccines across multiple studies. However, not all studies demonstrated a reduced antibody response to the administration of all vaccines. Variability in the results may be explained by differences in vaccinations tested, time elapsed between vaccination and antibody measurement, and means of analysis of antibody response. Reduction in antibody response to rubella, diphtheria, mumps, and tetanus vaccines reached statistical significance in some PFOA studies. Similarly, rubella, diphtheria, and mumps vaccine response was significantly lower in some PFOS studies. While further research needs to be done to verify and quantify this reduced antibody response, these findings suggest these vaccines may offer reduced protection to individuals with high concentrations of PFAS.

## **PFOA/PFOS and Antibody Response**

- There is strong evidence of antibody suppression with increased concentrations of both PFOA and PFOS in animal studies.
- Human studies suggest a similar pattern of reduced antibody response to specific vaccines with increasing concentrations of PFOA and PFOS.
  - Results were not consistent among studies for all vaccines
  - Reduced response demonstrated to rubella, diphtheria, mumps, and (for PFOA) tetanus vaccines



The International Agency for Research on Cancer (IARC) has classified PFOA as group 2B, possibly carcinogenic to humans, based on limited evidence in association to testicular and kidney cancers. EPA has concluded that both PFOA and PFOS are possibly carcinogenic to humans. Increased risk for certain types of cancer were found in communities and workers exposed to PFAS.

### **PFAS and Cancer**

- International Agency for Research on Cancer (IARC) has classified PFOA as possibly carcinogenic
- EPA has concluded that both PFOA and PFOS are possibly carcinogenic to humans.
- Increased risk for certain types of cancer were found in communities and workers exposed to PFAS



### Bladder Cancer

PFOs was evaluated in the perfluorooctanesulfonyl fluoride (POSF) studies out of Decatur, Alabama, and in the Danish population study. POSF-based products can be degraded or metabolized to PFOs. No association between PFOs and bladder cancer was observed in the Danish study. Elevated risks were observed in the Decatur worker studies but the evaluation of exposure-response trend was limited by a small number of cases, especially in the high exposure group. Although based on only three cases, a higher standardized mortality ratio (SMR) for bladder cancer was observed for employees with high exposure jobs. Possible limitations of these studies include not controlling for potential confounders including smoking. Based on these findings, there is limited but inconclusive evidence of an association between PFOs and bladder cancer. The association between PFOA and bladder cancer was evaluated in eight separate studies. Five studies found no association to incidence of bladder cancer and two studies found no association between PFOA and bladder cancer mortality. There was a negative trend observed for bladder cancer with a 10-year lag, based on a relatively small number of cases. Possible limitations include not controlling for potential confounders such as smoking. Based on these findings, there is no evidence of an association between PFOA and bladder cancer.

### Kidney Cancer

Exposure to PFOs and kidney cancer has not been evaluated. PFOA and kidney cancer has been

## **Occupational Exposure Studies and Cancer**

### **Bladder**

- Based on findings in the Cottage Grove and Decatur worker studies, there is inconclusive evidence of an association between PFOs and bladder cancer

### **Kidney**

- Findings in multi-site worker studies and the C8 population indicates evidence of an association between PFOA and kidney cancer

### **Pancreas**

- No evidence of an association between PFOs or PFOA and pancreatic cancer



evaluated in multiple studies. In one of these studies, no association was found between workers exposed to PFOA and kidney cancer. In two of the studies, workers with the highest exposure to PFOA were found to have an elevated SMR of kidney cancer when compared to those in the lowest exposure group. Kidney cancer incidence was elevated in the third quartile among the DuPont WV workers but not in the highest quartile. This could be due to the small number of cases in the highest exposure group. An additional study found an increased risk of cancer incidence in the highest exposed group. In the C8 population, the highest quartile of exposure also had an increased risk of kidney cancer. Based on these findings, there is some evidence of an association between PFOA and kidney cancer.

#### **Pancreatic Cancer**

The relationship between PFOS and pancreatic cancer was evaluated only in the Danish study and no association was found. Therefore, currently, there is no evidence of an association between PFOS and pancreatic cancer. PFOA was evaluated in three separate studies and no associations were found. Therefore, currently there is no evidence of an association between PFOA and pancreatic cancer.



### Prostate Cancer

The studies that evaluated PFOS include those conducted at the Decatur Alabama POSF plant, the study of a Danish cohort, and the case-control study of prostate cancer conducted in Sweden. Workers in the POSF plant had very high serum concentrations of PFOS but also high serum concentrations of PFOA, whereas the Danish and Swedish studies had substantially lower serum concentrations of both PFAS. Elevated risks were observed in the Decatur worker studies and the Danish study, but the studies were limited by very few cases. In the Swedish study, an elevated risk was observed only for those with above median PFOS concentrations who also had a first degree relative that also had prostate cancer. Both the Swedish study and the Danish study adjusted for BMI and smoking, both known risk factors for the disease. The Decatur worker study did not adjust for these risk factors. Based on the limitations of these data, there is inconclusive evidence of an association between PFOS and prostate cancer. PFOA was evaluated in the Danish and Swedish studies. Studies were also conducted on Ammonium pentadecafluorooctanoate (APFO) production workers at the 3M Cottage Grove plant, the Dupont West Virginia plant, and the C8 population, where the primary exposure was to PFOA. In addition, a study was conducted on workers exposed to APFO who were included in a multi-site study, one site being the Dupont West Virginia plant, where tetrafluoroethylene (TFE) was used. In the Cottage Grove studies, prostate cancer mortality was elevated but not prostate cancer incidence. In the Dupont West Virginia studies, elevated risks were

## **Occupational Exposure Studies and Cancer (cont'd)**

### **Prostate**

- Cottage Grove and WV studies demonstrate inconclusive evidence of an association between PFOA and prostate cancer.
- C8 and Swedish population studies demonstrate moderate evidence of an association between PFOA and prostate cancer.

### **Thyroid**

- Positive but inconsistent association between PFOA concentrations and thyroid cancer risk
- Limited evidence of an association between PFOA and thyroid cancer



observed for prostate cancer incidence but not mortality. Among the C8 population, one study based on self-reported and medically-confirmed cases found no association, but a second study based on cancer registry data observed elevated risks for those served by the Little Hocking water system and those with higher PFOA serum concentrations. Slightly elevated risks were also observed in the Danish and Swedish studies. In the Swedish study, the risk among those with above median serum PFOA concentrations who had a first degree relative with prostate cancer was elevated. Finally, the study of APFO workers in the TFE multi-site study had only three cases and did not observe an elevated risk. Given the findings in the Cottage Grove and Dupont West Virginia studies and supported from the findings in the C8 and Swedish population studies, there is some evidence of an association between PFOA and prostate cancer.

### Thyroid Cancer

Exposure to PFOS and thyroid cancer has not been evaluated. PFOA was evaluated among Dupont West Virginia workers and the C8 population. There was a positive but inconsistent association with PFOA levels and thyroid cancer risk; elevations in thyroid cancer incidence also occurred among the C8 population when comparing the highly exposed versus the less exposed, but the highest risks were in the 2nd and 3rd quartiles of exposure. Both of these studies suffered from very small populations. In external comparisons with the U.S. population, using a 10-year lag, there was no excess of thyroid cancer overall. Based on these studies, there is limited evidence suggesting correlation between thyroid cancer risk and PFOA.



although further research is needed to confirm this relationship.

PFAS are ubiquitous in both the U.S. and globally. There are no specific biomarkers of health effects caused by or linked to PFAS blood concentrations. The presence of PFAS in blood testing only confirms exposure, which is present in > 95% of the U.S. population based on representative samples from NHANES studies. While higher blood concentrations of PFAS suggest larger exposures, PFAS blood concentrations cannot be linked to any specific health effect(s), and results obtained from testing patients' blood PFAS concentrations would not guide medical decision-making. Even if a patient is identified as having an extremely high PFAS blood concentration, this does not mean he or she will suffer from any adverse health effects. Likewise, patients with mildly elevated PFAS blood concentrations are not immune from exposure-related health risks. Management of patients exposed to PFAS should be guided solely by patient symptoms and findings derived from a thorough health history and physical examination.

### **Blood Testing for PFAS**

- Human exposure to PFAS is ubiquitous in both U.S. and globally
- No specific biomarkers of clinical effects caused by PFAS
- Presence of PFAS in blood confirms past exposure (distant or recent), but does not indicate development of adverse health effects
- No specific blood PFAS concentrations will definitively cause any health effect



There is no health screening recommended because of PFAS exposure. However, as a part of the litigated settlement arising from the decades of exposure to PFOA-contaminated drinking water in the Parkersburg, West Virginia area, the C8 Medical Panel did identify specific health screenings associated with conditions identified as having a probable link to PFOA exposures. These will be presented on the next slide. Some of the C8 Medical Panel recommendations fall within routine care for some age groups but not all. Health histories addressing symptoms associated with the possible health effects identified by the C8 Medical Panel is one approach to monitor these potential health issues.

Let's look at the C8 Medical Panel recommendations.

### Screening for Disease

- There are no official guidelines supporting health screening for individuals exposed to PFAS.
- Some routine testing can provide information about associated health concerns, most notable cholesterol screenings.



**C8 Medical Panel: Screening By Age Recommendations**

Health Screening	15 years	15-18 years	18-19 years	20 or older years
High Cholesterol	●	●	●	●
Thyroid Disease	● / ● (at parents' discretion)	● / ● (at parents' discretion)	●	●
Ulcerative Colitis	●	●	●	●
Testicular Cancer	●	●	●	●
Kidney Cancer	●	●	●	●

**Pregnant Females**

● Blood pressure and urine protein should be measured at each prenatal visit – these tests are part of standard prenatal care

**Legend:**

● screening test indicated  
● screening by history/physical

The table presents the health screenings related to C8 health conditions and the age group that should be considered for each screening. Use of the C8 Medical Panel recommendations may be a topic of discussion between you and your patient. The recommendations made by the C8 Medical Panel call for screening for symptoms and discussing the risks and benefits of invasive testing with the patient prior to laboratory testing. Among these hypercholesterolemia, while asymptomatic, is screened for in the general population. The use of cholesterol screening under age 15 years is recommended in this table. However, the only guidelines to support this were made by an expert National Heart Lung and Blood Institute (NHLBI) panel. These NHLBI recommendations, endorsed by the American Academy of Pediatrics, call for cholesterol screening to occur between 9 and 11 years of age, and again between 17 and 21 years of age. No other invasive screening is recommended for pediatric patients unless patient symptoms of illness support further lab testing. Similarly, pregnancy-induced hypertension is screened for as a routine component of prenatal care. Presence of other C8-associated diseases such as thyroid disease and ulcerative colitis is assessed by monitoring for symptoms. Inclusion of questions focused on symptoms associated with these health concerns can be added to discussions with your patients. This symptoms-based inquiry can help to draw out new, worsening, or recurrent symptoms that your patient has that may need further evaluation and possible testing.



There are a lot of questions your patient may have about PFAS exposure and potential health effects. To respond to these questions, issues of uncertainty must be considered in your responses.

The next slide offers guidance on addressing uncertainty followed by slides that contain some of the questions in the PFAS Interim Guidance for Clinicians fact sheet. In the fact sheet patient questions are presented along with key messages and supporting facts you may consider using when answering patient questions.

## **POTENTIAL PATIENT QUESTIONS AND CLINICIAN RESPONSES**



As health care providers, you often face the challenge of discussing uncertainty of health impacts from disease and disease causations. This can be particularly difficult when the recommended course of action regarding a patient's concerns does not differ from standard care. Addressing uncertainty involves education on risks possibly related to an environmental exposure event, disease process, or medical intervention. Many studies and real-life situations have demonstrated that certain communication attributes allow for more effective and efficient communication. Key attributes of effective communication when discussing uncertainty include being clear and concise. Credibility and trust are necessary in patient care, and this requires effective listening and acknowledgement of patient concerns. It is also important to be willing to acknowledge what is factual and what is uncertain about potential health effects and how you can help your patient address the unknown. Use these opportunities to educate your patients about potential environmental health issues and provide guidance in risk reduction activities where appropriate.

## Addressing Patient Concerns

- Provide accurate information
- Be clear, concise, and willing to acknowledge uncertainties
- Listen to and address patient concerns
- Provide education concerning positive preventative health measures
- Provide guidance concerning relevant and feasible risk reduction activities



More than 95% of the represented U.S. population has measurable blood levels of PFOA and PFOS. The presence of these PFAS in blood only confirms exposure. This does not mean your patient will suffer any adverse health effects. Routine blood tests for PFAS cannot be extrapolated to any specific health effect(s) and cannot guide medical decision-making. Considering that the half-life of most PFAS compounds is several years, confirmation of PFAS in blood cannot be used to determine exposure source or time course. If your patient is seeking a PFAS blood test, the utility of the blood test results should be discussed so you and your patient can determine your course of action, especially as it impacts questions of uncertainty. Management of patients should be guided solely by findings from thorough patient histories and physical examinations. Serum PFAS concentrations may be assessed by public health officials to investigate community-wide exposure in order to understand the kinds and amounts of PFAS exposures in a given community and how these exposures compare to those in other populations. Serum PFAS measurements are most helpful when they are part of a carefully-designed research study.

### **Should I get Blood Testing for PFAS?**

- Presence of PFAS in blood only indicates exposure
- A serum concentration of PFAS can quantify current levels, but cannot predict health outcomes
- Routine testing for PFAS serves no clinical use and cannot guide medical decision-making
- Serum concentrations of PFAS may be assessed by public health officials to investigate population exposure



Extensive research has documented the broad and compelling advantages of breastfeeding for infants, mothers, families, and society. Some of the many benefits include immunologic advantages, lower obesity rates, and greater cognitive development for the infant as well as a variety of health advantages for the lactating mother. Even though a number of environmental pollutants, including PFAS, readily pass to the infant through human milk, the advantages of breastfeeding continue to greatly outweigh the potential risks in nearly every circumstance. It is currently recommended that nursing mothers continue to breastfeed their babies. The Pediatric Environmental Health Specialty Units (PEHSU) are a source of information about childhood exposures to toxic chemicals and other environmental hazards. The contact information for your regional PEHSU can be found at [www.pehsu.net](http://www.pehsu.net).

### **Is it Safe to Breastfeed?**

- Research clearly established the benefits of breastfeeding
- Advantages of breastfeeding outweigh the potential risks in nearly every circumstance
- Based on current knowledge it is recommended that mothers continue to breastfeed their babies
- For more information on childhood exposures to toxic chemicals and other environmental hazards, visit [www.PEHSU.net](http://www.PEHSU.net)



Techniques to enhance elimination of PFAS including phlebotomy and cholestyramine use have been investigated to reduce PFAS body burden. Research into these techniques is ongoing, but at present available literature does not support use of these interventions. Current studies are few and suffer from small sample sizes and lack of control populations, making it difficult to ascertain whether an appreciable increase in elimination or reduction of body burden of PFAS occurs with use. Furthermore, there is no evidence suggesting that the enhanced elimination that may be gained by utilization of these therapies offers any clinical benefit. As the therapies themselves are associated with risk, use of these techniques to attempt to mitigate PFAS-related health effects is not recommended. Mitigating disease risk due to chemical exposure requires identification and removal of the exposure source(s). Awareness and avoidance of potential sources of PFAS, as discussed earlier in this presentation, is a crucial first step. An exposed individual can further reduce his or her risk of disease by eliminating other factors for PFAS-linked conditions. For example, adhering to a healthy diet and regular exercise can decrease one's risk for high cholesterol, and abstinence from smoking can reduce one's risk of kidney cancer. Excessive supplementation of vitamins and minerals is not supported by literature to reduce disease risk attributable to PFAS and may cause toxicity, and is therefore not recommended. If a PFAS-linked clinical disease is diagnosed, a physician will determine appropriate treatment. Treatment guidelines for disease do not vary based on an individual's PFAS exposure.

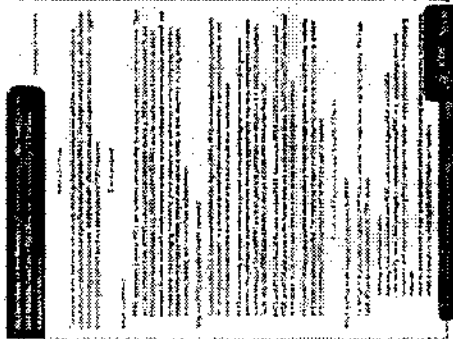
### **Are there treatments available for PFAS exposure?**

- Therapies intended to reduce body burden by enhancing elimination of PFAS are not recommended
- Mitigating risk of disease involves reducing PFAS exposure and minimizing other disease risk factors
- Standard treatment for diseases possibly linked to PFAS should not vary based on an individual's blood PFAS test results or amount of PFAS in drinking water, indoor dust, etc.



For more potential patient questions and key messages, please refer to the ATSDR document: An Overview of Perfluoroalkyl and Polyfluoroalkyl Substances and Interim Guidance for Clinicians Responding to Patient Exposure Concerns. The purpose of this fact sheet is to aid physicians and other clinicians with patient consultations on PFAS. It highlights what PFAS are, specifies which chemicals fall into this category of substances, identifies health effects associated with exposure to various PFAS, and suggests answers to specific patient questions about potential PFAS exposures and health concerns.

## More Patient Questions/Answers





Finally, we wish to point out a few resources that can be helpful to clinicians. These include the Pediatric Environmental Health Specialty Units (PEHSU). The PEHSU are a national network of experts available to provide consultation and education to clinicians and communities wishing to learn more about PFAS and other hazardous substances. These units are staffed by clinicians with environmental health expertise in pediatrics, reproductive health, occupational and environmental medicine, medical toxicology, and other related areas of medicine. There is no cost to you for calling upon the PEHSU for education and consultation about environmentally-exposed patients, including those impacted by PFAS.

Thank you for attending this presentation regarding per- and polyfluoroalkyl substances. To access other materials regarding environmental health concerns, please visit ATSDR's "Resources for Health Professionals."

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*This presentation is designed to assist clinicians by offering peer-reviewed, up-to-date literature about PFAS and how to deal with patient management and treatment after PFAS exposure. It highlights what PFAS are, which chemicals fall into this category of substances, identifies health effects associated with exposure to various PFAS, and suggests answers to specific patient questions about potential PFAS exposure.*

## Additional Information

Resource	URL
ATSDR PFAS portal	<a href="http://www.atsdr.cdc.gov/pfas/index.html">http://www.atsdr.cdc.gov/pfas/index.html</a>
CR Science Panel	<a href="http://www.ccrsciencepanel.org/jrnp-joint.html">http://www.ccrsciencepanel.org/jrnp-joint.html</a>
EPA PFAS	<a href="http://www.epa.gov/chemical-research/research-special-chemicals-additional-chemicals-and-chemicals">http://www.epa.gov/chemical-research/research-special-chemicals-additional-chemicals-and-chemicals</a>
IARC	<a href="http://www.iarc.fr/">http://www.iarc.fr/</a>
NIH/NIH/NIH	<a href="http://www.nih.gov/health/materials/pfas/chemicals-chemicals-30.pdf">http://www.nih.gov/health/materials/pfas/chemicals-chemicals-30.pdf</a>
Pediatric Environmental Health Specialty Units (PEHSU)	<a href="http://www.pedhsu.net/">http://www.pedhsu.net/</a>